Title of the project

QAngio XA 3D/QFR and CAAS vFFR imaging software for assessing coronary obstructions: a systematic review and economic evaluation

Name of External Assessment Group (EAG) and project leads

Centre for Reviews and Dissemination and Centre for Health Economics - York EAG

Dr Mark Simmonds
Centre for Reviews and Dissemination
University of York

Dr Claire Rothery
Centre for Health Economics
University of York

Plain English Summary

Stable angina is a type of chest pain caused by insufficient blood supply to the heart, brought on by physical activity or emotional stress, which goes away with rest. If left untreated, it can lead to complications such as unstable angina, heart failure, heart attack, and sudden death.

To avoid these complications, patients may require intervention to open damaged, constricted or blocked arteries, known as “revascularisation”. This most commonly consists of inserting a small tube or “stent” into the artery to keep it open and allow blood flow.

Patients who might need revascularisation undergo a number of tests to identify blocked arteries, including coronary computed tomography angiography (CCTA) and other non-invasive tests. However, these tests are often inconclusive, in which case more invasive tests are needed.

The last line of testing consists of an invasive coronary angiogram (ICA). During an ICA procedure, a catheter is inserted into an artery and moved into the coronary arteries. A special type of dye called contrast medium is injected through the catheter and X-ray images (angiograms) are taken. Visual assessment of these angiograms has limited ability to differentiate between arteries with inadequate blood supply (which need revascularisation) and those with adequate supply which do not need treatment. When an angiogram is inconclusive it may be combined with the invasive measurement of blood flow, measured by inserting a wire into the artery, after giving drugs to dilate the artery. This is called invasive fractional flow reserve (FFR) assessment. Because this procedure is invasive it carries some risks and may have substantial side effects.

Non-invasive imaging tests have been proposed to precede or replace invasive FFR, by using the existing angiograms to determine blood flow, without inserting a wire. These include the QAngio XA 3D/QFR imaging software (produced by Medis) and CAAS vFFR (produced by Pie Medical Imaging).

This project will investigate whether the QAngio and CAAS vFFR technologies can provide accurate assessments of blood flow. The project will consider whether these technologies can improve on using visual assessment of the angiograms alone, and be used to make reliable decisions on whether revascularisation is needed, and so reduce the need for invasive FFR. It will also investigate whether using these technologies is a reasonable use of NHS resources.

To do this a thorough review of all the literature on the QAngio and CAAS vFFR technologies will be performed. Any data from studies of these technologies will be re-analysed to determine whether it accurately predicts the need for revascularisation and consider its clinical benefits. An economic analysis will be conducted to investigate whether using either of these technologies is economically viable.

Decision problem

The purpose of this assessment is to investigate non-invasive technologies for assessing the functional significance of coronary stenoses during invasive coronary angiography (ICA). This may be either quantitative flow ratio (QFR) assessment using the QAngio XA 3D/QFR (Medis) imaging software or vessel-fractional flow reserve using the CAAS vFFR system (Pie Medical Imaging). The assessment will consider whether these are clinically useful and cost-effective as alternatives to, or in addition to, using standard ICA alone, with or without invasive assessment of fractional flow reserve.

Interventions

Non-invasive imaging techniques for the assessment of the functional significance of coronary obstructions (stenoses) avoid the need for a pressure wire or adenosine. They could be used in people with stable chest pain of recent onset who are referred for invasive coronary angiography (ICA). Visual assessment of angiograms taken during ICA may be limited in its ability to differentiate between functionally significant (causing inadequate blood supply) and non-significant (not significantly affecting blood supply) coronary stenoses.

QAngio XA 3D/ QFR

QAngio XA 3D/QFR (Medis) imaging software is used to perform QFR assessment of coronary artery obstructions. It is designed to be used with all invasive coronary angiography (ICA) systems; biplane or monoplane. It uses 2, 2D X-ray angiographic projections, taken at least 25 degrees apart – and ideally between 35 and 50 degrees apart – to create a 3D-reconstruction of a coronary artery; this shows the QFR values across the artery. QFR is an assessment (by frame count) of the pressure (blood flow velocity) drop over the artery, with a value of 1 representing a normally functioning artery with no pressure drop. A 20% or more drop in blood pressures (QFR value of 0.8 and less) is considered a significant obstruction where revascularisation should be considered. QAngio XA 3D/QFR software is installed on a laptop or workstation that is connected to the ICA system. The Digital Imaging and Communication in Medicine (DICOM) data from ICA projections are immediately uploaded and viewable on the connected workstation. The total time for data acquisition and analysis is about 4 to 5 minutes (as reported by the company). AngioPlus (Pulse Medical Imaging Technology, Shanghai, China) is an equivalent CE-marked version marketed in Asia.

The QAngio software offers two different flow models to calculate QFR:

- Fixed flow QFR, using fixed flow velocity
- Contrast QFR, using contrast frame count in an angiogram without hyperaemia.

Fixed flow QFR is faster to compute, but may be less accurate than contrast QFR.

Furthermore, the QAngio software provides 4 different QFR indices along the analysed coronary segment:

- Vessel QFR: the QFR value at the distal location of the analysed vessel segment
- Index QFR: a point which can be moved along the QFR pullback curve
- Lesion QFR: the contribution to the QFR drop by the selected lesion alone

- Residual vessel QFR: an indication of the vessel QFR, if the selected lesion is resolved.

CAAS vFFR

CAAS vessel-FFR workflow builds a 3D reconstruction of a coronary artery based on 2 standard X-ray angiograms, assesses the pressure drop across the stenosis, and determines a vessel FFR value. It gives both anatomical and functional assessment of the stenosis, and can be integrated into catheter laboratories. The total time for analysis is approximately 2 minutes per artery according to the company.

All available versions of CAAS (8.0, 8.1, 8.2) use the same algorithm for calculating vFFR. The CAAS workstation provides various modules (for example, quantitative coronary arteriography and left ventricular analysis), and the vFFR module can be added to the CAAS workstation. In addition to the vFFR, CAAS vFFR provides measurements at the end of the lesion and at a chosen position in the coronary artery.

Diagnostic technologies and pathways

The main alternatives to using QAngio or CAAS vFFR , are:

a) Visual interpretation of the angiographic images created during invasive coronary angiography (ICA) (including assessment of percentage diameter stenosis), without invasive flow assessment (FFR or iFR).
b) Visual interpretation of the angiographic images, followed by invasive flow assessment (FFR or iFR) if ICA alone is inconclusive.

Therefore, when adding the option to use QAngio or CAAS vFFR , four diagnostic pathways might be used to decide on whether to proceed to revascularisation, namely:

1. Visual assessment of ICA alone (without QFR or FFR/iFR)
2. ICA, followed by FFR/iFR if ICA is inconclusive
3. ICA, followed by QFR or vFFR if ICA is inconclusive (without using FFR/iFR)
4. ICA, followed by QFR or vFFR if ICA is inconclusive, with subsequent FFR/iFR if results remain inconclusive

The clinical and cost-effectiveness of each of these four diagnostic pathways will be investigated and compared.

Population and relevant subgroups

The population of interest is individuals with suspected stable angina who may need revascularisation, who have been referred for ICA because any previous non-invasive testing has not resolved whether revascularisation is required.

According to NICE guidance, ICA should be a third-line assessment: following CT coronary angiography and/or other non-invasive functional imaging, where these have not resolved whether revascularisation is required. However, ICA may also be used as a first or second-line assessment where CT coronary angiography is unavailable, or if patients are deemed at sufficiently high risk for revascularisation to justify immediate ICA.

The particular focus is on patients whose ICA results show intermediate stenoses. Various definitions of intermediate stenosis exist, with lower limits ranging from 30% to 50% and upper limits from 70% to 90%. This assessment will therefore not, initially, use any specific definition, instead considering an intermediate stenosis to be any stenosis where uncertainty remains before or after ICA as to whether revascularisation should be performed.

The accuracy of QFR or vFFR in identifying individuals who may require revascularisation may depend on some clinical and lesion characteristics such as age, gender, history of cardiovascular disease, previous PCI, lesion length and location. Previous MI and presence of microcirculatory disease have been identified as variables that may be associated with reduced accuracy of QFR.[1-3] The subgroups relevant to this appraisal can be defined as people at higher (and lower) risk of requiring revascularisation.

Place of the intervention in the care pathway

Angina is a type of chest pain caused by insufficient blood supply to the heart (myocardial ischemia). Stable angina is brought on by physical activity or emotional stress, and goes away with rest. It is the key symptom of coronary artery disease which remains one of the main causes of morbidity and mortality in high-income countries. If left untreated, it can lead to cardiovascular complications such as, unstable angina, myocardial infarction, heart failure and sudden cardiac death.

The diagnostic pathway for stable angina aims to confirm the diagnosis of stable angina, and define the severity of coronary stenosis to identify people who may benefit from revascularisation in addition to optimal medical therapy.

Patients who experience chest pain will be assessed for angina, and other cardiovascular conditions. Where clinical assessment alone is insufficient for a diagnosis patients should be referred for 64-slice or above coronary CT angiography (CCTA) as the first-line diagnostic test when clinical assessment suggests typical or atypical angina, or non-anginal chest pain, but 12-lead resting electrocardiogram (ECG) has been done and shows ST-T changes or Q waves.

Patients may go on to further diagnostic testing. NICE guidance recommends offering non-invasive functional imaging for myocardial ischaemia if 64-slice or above CCTA has shown coronary artery disease of uncertain functional significance, or is non-diagnostic. This could include:

- myocardial perfusion scintigraphy with single-photon emission computed tomography (MPS with SPECT)
- stress echocardiography
- first-pass contrast-enhanced MR perfusion
- MR imaging for stress-induced wall motion abnormalities.

If these tests are also inconclusive ICA is offered as a third-line diagnostic tool.

A diagnosis of stable angina should be made when clinical symptoms are present and:

- significant coronary artery disease is found during ICA or 64-slice (or above) CTCA. This is usually defined as 70% or more diameter stenosis of at least one major epicardial artery segment or 50% or more diameter stenosis in the left main coronary artery.
- reversible myocardial ischaemia is found during non-invasive functional imaging.

ICA may also be used to guide treatment strategy for people with a confirmed diagnosis of stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment, and so may require revascularisation.

During an ICA procedure, a coronary diagnostic catheter is inserted into an artery, usually in the arm pit or groin, and moved up the aorta and into the coronary arteries. A special type of dye called contrast medium is injected through the catheter and X-ray images (angiograms) are taken. Although providing valuable information on coronary artery anatomy, visual assessment of angiograms taken during ICA has limited ability to differentiate between functionally significant (causing inadequate blood supply) and non-significant (not significantly affecting blood supply) coronary stenoses.

When ICA is used to determine the presence and severity of coronary stenosis, it may be combined with the invasive measurement of FFR using a pressure wire. NICE guideline on chest pain does not currently consider FFR; however other guidelines (such as those of the European Society of Cardiology and American College of Cardiology) do recommend its use, and state that lesions with an FFR of less than 0.80 are functionally significant and revascularisation may be considered. FFR is assessed invasively by advancing a pressure wire towards the stenosis and measuring the ratio in pressure between the two sides of the stenosis during maximum blood flow (induced by adenosine infusion). This is associated with risks related to the passage of a guide wire, side effects of adenosine, and additional radiation exposure. The invasive FFR measurement is also associated with increased procedural time and costs, compared with ICA alone.

As an alternative to invasive FFR, instantaneous wave-free ratio (iFR) may be used. This also uses inserted pressure wires to assess flow, but does not require vasodilator drugs such as adenosine. An iFR of 0.89 or less is considered functionally significant.

ICA can be performed either in diagnostic-only ICA laboratories, or in interventional catheter laboratories as part of the initial stenosis assessment prior to percutaneous coronary intervention. In diagnostic-only laboratories patients where ICA alone is inconclusive might be referred to an interventional laboratory for an FFR or iFR assessment. In interventional laboratories an FFR or iFR assessment can be performed immediately after ICA, if needed.

QFR or vFFR could potentially replace pressure-wire FFR, or iFR, by providing a non-invasive means to assess FFR as part of an ICA assessment. Alternatively, they may be used as a precursor to invasive FFR, with the invasive procedure used when QFR or vFFR is inconclusive. The QAngio instructions recommend the following approach:

- QFR below 0.78: treat the patient in the catheter laboratory;
- QFR above 0.84: follow the patient medically;

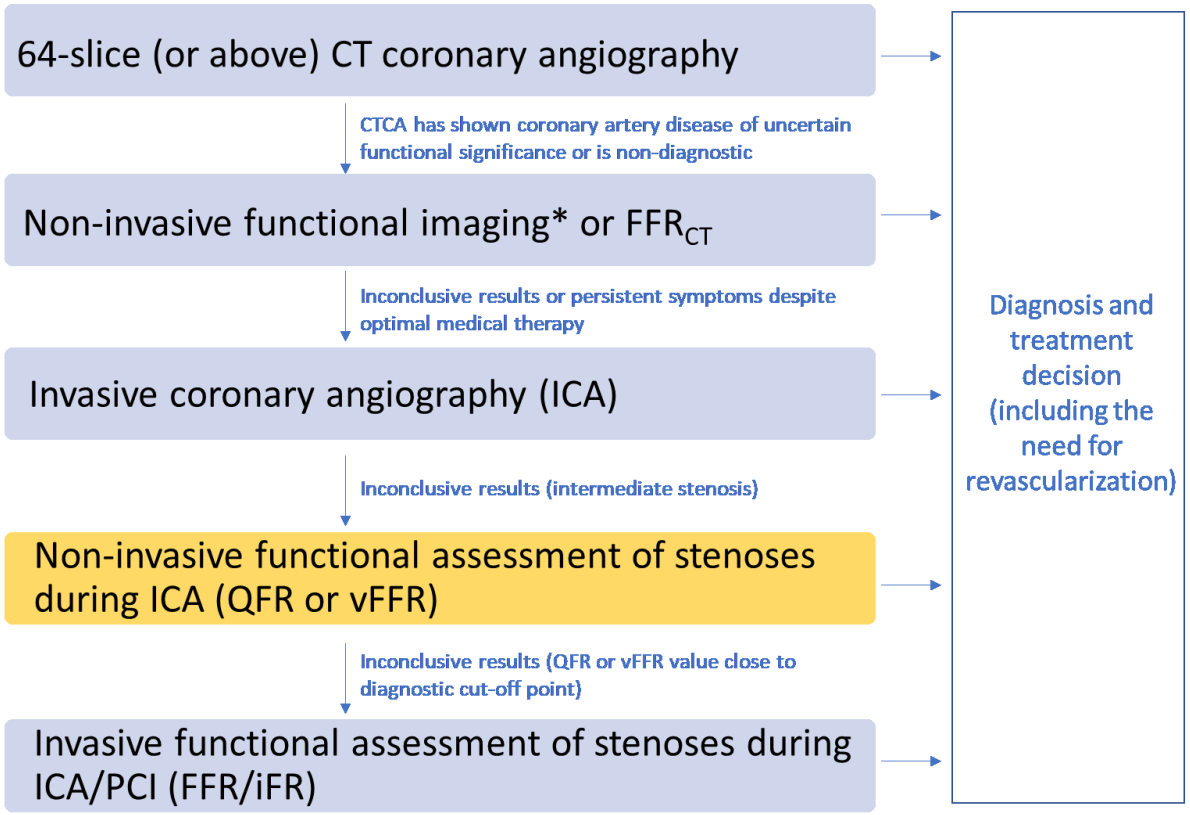
- QFR between 0.78 and 0.84: verify by invasive FFR measurement.

QFR could also potentially be used in other aspects of decision making, including whether to stent more than one vessel, or to select a stent type or other interventional device for revascularisation.

QAngio and CAAS vFFR could be used in diagnostic-only laboratories, possibly reducing the need for referrals to interventional laboratories.

The likely pathway leading to invasive FFR, and including the probable placement of QFR, is summarised in Figure 1.

Figure 1: Diagnostic pathway for stable angina, including QFR or vFFR (from NICE DAP 48 final scope)



A diagnosis of stable angina should be made when:

- significant coronary artery disease is identified during ICA or 64-slice (or above) CTCA, usually defined as 70% or more diameter stenosis of at least one major epicardial artery segment or 50% or more diameter stenosis in the left main coronary artery.
- reversible myocardial ischaemia is found during non-invasive functional imaging

There is substantial regional variation in the diagnostic pathway for stable angina, due in part by availability of imaging modalities at each centre, and experience (or preferences) of the cardiologists

referring for the test. Clinical advisors noted that the pathway recommended by NICE is widely recognised as current best practice.

Objectives

The aim of the project is to determine the clinical and cost-effectiveness of non-invasive assessment of the functional significance of coronary stenoses, using the QAngio XA 3D/QFR (Medis) and CAAS vFFR (Pie Medical Imaging) imaging software.

To achieve this, the following objectives are proposed:

Clinical effectiveness

- To perform a systematic review and meta-analysis of the diagnostic accuracy and, where feasible, clinical efficacy of the QAngio XA 3D/QFR imaging software, and CAAS vFFR software, used during ICA for assessing the functional significance of coronary obstructions in people with stable chest pain whose angiograms show intermediate coronary stenosis.
- To perform a narrative systematic review of the clinical efficacy and practical implementation of QAngio and CAAS vFFR. This will include assessment of the associated revascularisation rates, mortality and morbidity, patient-centred outcomes, adverse events, and acceptability to clinicians and patients.

Cost-effectiveness

- To perform a systematic review of published cost-effectiveness studies of the use of the QAngio XA 3D/QFR imaging software, and CAAS vFFR software, for assessing the functional significance of coronary stenosis in people with stable chest pain whose angiograms show intermediate stenosis.

- To develop a decision model to estimate the cost-effectiveness of the QAngio XA 3D/QFR and CAAS vFFR imaging software used during ICA to indicate whether coronary obstructions are functionally significant. Consideration will be given to differences in the cost-effectiveness of the technologies in diagnostic-only or in interventional catheter laboratories.

- The decision model will link the diagnostic accuracy of QFR derived from the QAngio XA 3D/QFR imaging software, and vFFR derived from the CAAS vFFR software, to short-term costs and consequences (e.g., the impact on the number of revascularisations needed, the proportion of people who need invasive functional assessment of stenosis, time to test results, and associated risks of the diagnostic intervention). It will then link the short-term consequences to potential longer-term costs and consequences (e.g., major cardiovascular events such as myocardial infarction and sudden cardiac death, adverse events related to revascularisation and diagnosis, mortality) using the best available evidence.

- The cost-effectiveness of the QAngio XA 3D/QFR and CAAS vFFR imaging software compared with visual assessment of ICA alone, or ICA followed by FFR/iFR if ICA is inconclusive, will be expressed in terms of incremental cost per quality-adjusted life year and/or net health (or monetary) benefits.

Methodology

Systematic review of diagnostic accuracy and clinical effectiveness

The systematic review will be conducted following the general principles recommended in CRD's guidance and reported in accordance with the PRISMA statement.

Literature searching

Comprehensive searches of the literature will be conducted to identify all studies relating to the QAngio technology and to CAAS vFFR.

Focused searches will be used to identify literature on invasive FFR more generally, to identify key papers and reviews of the clinical effectiveness and implementation of invasive pressure-wire FFR and iFR.

The following databases will be searched: MEDLINE, PubMed, EMBASE, Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), CENTRAL, Health Technology Assessment (HTA) Database and EconLit.

Ongoing and unpublished studies will be identified by searches of ClinicalTrials.gov, Conference Proceedings Citation Index: Science, EU Clinical Trials Register, Open Access Theses and Dissertations, Proquest Dissertations & Theses A&I, PROSPERO, WHO International Clinical Trials Registry Platform portal and manufacturer websites. Abstracts from any recent conferences which are thought to be relevant to the review will also be consulted.

A search strategy for Ovid MEDLINE is included in Appendix 1. The MEDLINE strategy will be translated to run appropriately on the other databases and resources. No language or date restrictions will be applied to the searches. A study design search filter will not be used.

Reference lists of relevant reviews will be scanned in order to identify additional potentially relevant reports.

Searches for studies for cost and quality of life data will also be undertaken, as determined by the economic model.

Pragmatic supplementary searches for primary and secondary data (including existing systematic reviews) will be carried out as necessary, depending on the gaps and limitations identified during the review of clinical and economic evidence and during the development of the model.

IPD and contact with study authors and manufacturers

An individual participant data (IPD) meta-analysis of four studies likely to be eligible for this review has previously been performed.[4] The EAG have contacted the authors, and they have agreed, in principle, to share the collected IPD with the EAG for the purposes of this assessment.

Given this agreement, the authors of any other diagnostic accuracy studies deemed eligible for the review may also be contacted and IPD for their study requested. However, given the short timelines of this project, IPD requests will be restricted to larger studies of most relevance to UK. It is also anticipated that authors may not be able to provide IPD, and published data will be used. IPD will not be sought for studies of clinical outcomes.

It is anticipated that many studies may not report sufficient data in publications to perform full syntheses or fully populate the economic model. Therefore, study authors may be contacted to seek detailed diagnostic and other clinical data as appropriate, where they are unable to provide suitable IPD. Manufacturers may similarly be contacted to seek more detailed data, and to identify unpublished studies or data sources.

Study selection

Two reviewers will independently screen all titles and abstracts. Full papers of any titles and abstracts that may be relevant will be obtained where possible, and the relevance of each study assessed independently by two reviewers according to the criteria below. Any disagreements will be resolved by consensus or, where necessary, by consulting a third reviewer. Conference abstracts will be eligible and attempts will be made to contact authors for further data.

The following eligibility criteria will be used to identify relevant studies:

Participants

Patients with stable chest pain (either suspected stable angina or confirmed angina that is not adequately controlled by treatment), who are referred for ICA to assess coronary stenosis and the need for revascularisation. Studies without patients with intermediate stenosis (however defined) will be excluded.

Interventions

QAngio XA 3D/QFR (and AngioPlus) and CAAS vFFR imaging software used in conjunction with ICA to allow simulation of FFR.

The two sub-measurements of contrast-flow QFR (cQFR) and fixed-flow QFR (fQFR) that are offered by the QAngio software will be included. Eligible healthcare settings include diagnostic-only and interventional catheter laboratories.

Reference standard

The reference standard is FFR assessed using an invasive pressure wire with or without adenosine.

Instantaneous wave-free ratio (iFR), which was found to be non-inferior to FFR,[5] will also be accepted as a reference standard.

Outcomes

The eligible outcome measures relating to diagnostic accuracy are:

- Sensitivity and specificity of QAngio XA 3D/QFR, CAAS vFFR
- Positive and negative predictive values
- Estimates of difference in measurements between QFR or vFFR and invasive FFR/iFR
- Correlation between QFR or vFFR and invasive FFR/iFR measurements (including Bland-Altman assessments)

Some studies may report difference or concordance between QFR or vFFR and invasive FFR/iFR in numerous ways, including inter and intra-rater differences in measurements, correlation coefficients, sensitivity and specificity or ROC curves. All relevant outcome definitions and cut-offs will be extracted and their applicability to the decision problem will be accounted for when presenting the results. Diagnostic accuracy results of ICA alone will be considered if reported alongside QAngio or CAAS.

In addition, the following clinical outcomes will be eligible:

- Morbidity, mortality and major adverse events (e.g. myocardial infarction, heart failure)
- Adverse events related to the diagnostic procedure (e.g. pressure wire damage, adenosine side effects, stroke)
- Adverse events related to revascularisation
- Distress, anxiety and similar harms caused by QFR, vFFR, invasive FFR or iFR
- Subsequent use of invasive pressure-wire FFR or iFR
- Subsequent revascularisation procedures performed
    - Including unscheduled revascularisations
- Number of vessels with stent placements
- Health related quality of life
- Radiation exposure
- Test failure rates
- Inconclusive test rates
- Inter-observer variability

Eligible outcomes related to the implementation of the interventions of interest and related practical issues include:

- Acceptability of QFR, vFFR and invasive FFR (to clinicians and patients)
- Timing of results from data acquisition
- Referral times
- Patient satisfaction
- Training requirements
- Uptake and compliance

Study designs

Diagnostic accuracy and correlation studies

Eligible study designs will be studies in which QFR using the QAngio system, or CAAS vFFR are performed alongside invasive FFR (or iFR) as a reference standard in the same patients.

Clinical effectiveness/implementation

Eligible study designs will be any experimental or observational study where QFR or vFFR (with or without invasive FFR) have been used and which report relevant clinical outcomes as listed above. We will also include relevant publications reporting issues related to implementation of, or practical advice for, QFR or vFFR and their use in clinical practice.

The following types of publication will be excluded: case reports, and studies focusing only on technical aspects of QFR or vFFR (such as technical descriptions of the testing process or specifications of machinery and software).

Data extraction

Data on study and patient characteristics and results will be extracted by one reviewer using a standardised data extraction form and independently checked by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer where necessary. If time constraints allow, attempts will be made where possible to contact authors and/or manufacturers for missing data and original raw data (IPD). Data from relevant studies with multiple publications will be extracted and reported as a single study. The most recent or most complete publication will be used in situations where we cannot exclude the possibility of overlapping populations.

Where IPD cannot be supplied, data may be extracted from published figures using suitable data extraction software.

Collection of IPD

In order to obtain IPD a data sharing agreement will be established between study authors and the EAG (see draft version in Appendix 2) to permit formal transfer of data. Data will be requested on results of QFR, invasive FFR, and ICA, sufficient to calculate diagnostic accuracy, along with data on key subgroup characteristics (see below), where available; however the EAG will accept any data the authors may have. The EAG will accept data in any electronic form. Data supplied must be anonymised and transferred to the EAG by secure means. The data will be held securely at York, accessible only to the EAG, and will not be transferred to other computers or portable devices. IPD will be deleted after the end of the project, in agreement with study authors.

Quality assessment strategy

The quality of the diagnostic accuracy studies will be assessed using the QUADAS-2 tool (Quality Assessment tool of Diagnostic Accuracy Studies), modified as necessary to incorporate review-specific issues. QUADAS-2 evaluates both risk of bias and study applicability to the review question. Suitable quality assessment tools such as ROBINS-I will be used based on the availability of other eligible clinical outcomes and study designs.

The quality assessments will be performed by one reviewer and independently checked by a second reviewer. Disagreements will be resolved through consensus, and where necessary, by consulting a third reviewer.

Synthesis

In the initial synthesis, the results of data extraction will be presented in structured tables and as a narrative summary, grouped by population and test characteristics. Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques.

Statistical analysis of diagnostic accuracy

Using extracted diagnostic accuracy data from 2 x 2 tables, from IPD, or extracted from figures, estimates of sensitivity and specificity will be calculated and presented on forest plots and in the receiver operating characteristic (ROC) space to examine the variability in diagnostic test accuracy within and between studies. Positive and negative predictive values will also be calculated and presented in figures and tables. Where three or more studies are available the hierarchical bivariate model described by Reitsma et al. will be fitted which calculates summary estimates of sensitivity and specificity and the associated 95% confidence intervals (CIs). The hierarchical summary ROC (HSROC) model will also be fitted to produce summary ROC curves. Results of both models will be presented in ROC plots.

While diagnostic accuracy analysis will be the preferred method of meta-analysis, if this is not feasible meta-analysis of correlation coefficients and meta-analyses of differences in measurements will also be performed.

Sensitivity analyses will be performed to assess the possible impact of uncertainty in diagnostic accuracy, differences across patient subgroups, and the impact of failed or inconclusive QFR assessment.

Statistical analysis of clinical effectiveness

Data on clinical outcomes will be tabulated or plotted. Where there are sufficient studies reporting the same clinical outcomes, results will be synthesised using standard random-effects meta-analyses.

If sufficient data are available, statistical models (such as simulation studies) will be generated to assess the impact of QFR, vFFR and invasive FFR/iFR assessment on the number of revascularisations performed, and on morbidity and mortality and other longer-term outcomes. The four diagnostic pathways:

1. Visual assessment of ICA alone (without QFR or FFR/iFR)
2. ICA, followed by FFR/iFR if ICA is inconclusive
3. ICA, followed by QFR or vFFR if ICA is inconclusive (without using FFR/iFR)
4. ICA, followed by QFR or vFFR if ICA is inconclusive, with subsequent FFR/iFR if results remain inconclusive

will be compared in terms of their impact on morbidities, mortality and adverse events.

All statistical analyses will be conducted in R and/or Stata software, as appropriate.

Investigation of heterogeneity and subgroup analyses

For diagnostic accuracy data, we will visually inspect the forest plots and ROC space to check for heterogeneity between study results. To investigate sources of heterogeneity, we will incorporate relevant covariates in the bivariate and HSROC models, where possible. Subgroup analyses will be conducted, by performing separate bivariate and HSROC models in defined subgroups of studies.

Where possible, for diagnostic accuracy data and clinical outcomes reviews, we will consider the following factors as potential sources of heterogeneity:

- Type and severity of stenosis (e.g. high percentage diameter stenosis)
- multivessel coronary artery disease
- diffuse coronary artery disease
- multiple stenoses in one vessel
- microvascular dysfunction (for example, caused by diabetes)
- chronic total occlusion
- diabetes
- sex
- age
- ethnicity (or study location as a proxy for ethnicity)
- results of previous non-invasive tests
- use of fixed flow QFR vs. contrast QFR (QAngio XA 3D)
- previous MI

Sensitivity analyses

We will carry out sensitivity analyses to explore the robustness of the results according to study quality based on QUADAS-2 domain results (for example, by excluding studies with high risk of incorporation bias) and study design (for example, in-procedure versus retrospective evaluation of index test results) for diagnostic accuracy studies.

Where participants from several studies are recruited from the same cohorts and significant overlap is suspected, data from only one study with the most reliable reporting will be included in the main analyses. The impact of studies where substantial overlap is suspected, or where only a composite outcome is reported, will be explored by including/excluding them from the main analyses.

Narrative synthesis

For outcomes related to clinical effectiveness and implementation of QFR, vFFR and invasive FFR, and where meta-analysis is not feasible, we will perform a narrative synthesis. For this we will extract summary information on the findings of included studies that relate to the clinical and implementation outcomes and summarise and harmonise these across studies. Also considered will be: the conclusions of these studies, suggested consequences for QFR and ICA, recommendations for practice and suggested needs for further research. These results will be tabulated and summarised.

Narrative summaries will be used for any outcomes where meta-analyses or other statistical analyses are not feasible. This will include tabulating or plotting results as reported in studies, and narratively describing and comparing these results.

Additional clinical evidence

Depending upon the findings from the clinical and cost-effectiveness review, it may be necessary to undertake additional targeted searches to inform the risks of major cardiovascular events and associated costs and outcomes in order to properly inform and conduct the economic model. If this is considered necessary, the review will, initially, be restricted to published cost-effectiveness models that assess the long-term impact of diagnostic strategies in the management of coronary artery disease (CAD) and/ or predict costs and outcomes in CAD from a UK perspective. If data gaps are still evident, a pragmatic approach will be used, supplementing findings with targeted searches for systematic reviews, long-term RCTs with clinical outcomes and/or prospective cohort studies.

Systematic review of cost-effectiveness evidence and development of decision model

Relevant cost-effectiveness evidence on the use of the QAngio XA 3D/ QFR imaging software and CAAS vFFR (Pie Medical Imaging) for the assessment of coronary obstructions will be systematically identified, appraised for quality and narratively summarised. The aim of the review will be to examine any existing decision-analytic models used to assess the cost-effectiveness of QAngio XA 3D/ QFR and CAAS vFFR against any comparator(s), in order to identify key issues and areas of uncertainty that could be addressed in the development of a new decision-analytic model for this assessment.

Systematic review of cost-effectiveness evidence

The results of the searches carried out for the systematic review of clinical effectiveness and diagnostic accuracy of the QAngio XA 3D/ QFR and CAAS vFFR imaging software will be used to identify any relevant studies of the cost-effectiveness of the technology against its relevant comparators. A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside clinical trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature.

The main findings of existing economic evaluations will be narratively summarised and tabulated for comparison within the text of the report. In particular, information will be extracted on the comparators, study population and setting, main analytic approaches (e.g. patient-level analysis / decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality-of life, direct costs and indirect costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic / probabilistic sensitivity analysis).

The review will examine existing decision-analytic models in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. This review will be used to identify the central issues associated with adapting existing decision models to address the current decision problem and to assist in the development of a new decision model drawing on the issues identified in the clinical and cost-effectiveness review.

Initial scoping searches indicate that the existing cost-effectiveness literature for the QAngio XA 3D/ QFR and CAAS vFFR imaging software is likely to be limited. Therefore, to further inform the development of a new decision-analytic model, we will also undertake a targeted literature search to identify cost-effectiveness studies evaluating ICA in people with stable chest pain of recent onset. The inputs and assumptions in these studies may be important to consider as part of the conceptualisation and development of a new decision model. These studies will not be subject to a formal assessment but will be used, as necessary, to assist in the overall development of a new decision-analytic model for the evaluation of QAngio XA 3D/ QFR and CAAS vFFR imaging software.

In particular, they will be used to identify important parameter estimates and source of data inputs, as well as highlighting key areas of uncertainty.

Development of a de-novo economic model

Following the review of existing cost-effectiveness evidence, a decision-analytic model will be developed. This will aim to estimate the cost-effectiveness of the QAngio XA 3D/ QFR and CAAS vFFR imaging software used during ICA for the assessment of coronary obstructions in people with stable chest pain whose angiograms show intermediate stenosis. Consideration will be given to differences in the cost-effectiveness of the technologies in diagnostic-only or in interventional catheter laboratories. The population, comparator technologies and reference standards are as set out above.

The model will be populated using results from the systematic clinical effectiveness review, other focused reviews to inform key parameters (e.g., health-related quality of life utility values), routine sources of cost data, and if necessary additional study specific cost estimates provided by experts and/or relevant investigators.

The model will be developed in accordance with the NICE reference case. The perspective will be that of the National Health Services and Personal Social Services, health benefits will be expressed in terms of quality-adjusted life years (QALYs) and both costs and quality-adjusted life years discounted at a rate of 3.5% per annum.

General structure of the model

Diagnostic outcomes will be modelled with a decision tree, which takes account of the diagnostic accuracy of the non-invasive tests (ICA without the functional assessment of coronary obstructions and QAngio XA 3D/ QFR and CAAS vFFR used during ICA) relative to the reference standard test of invasive FFR/iFR measurement using pressure-wire (assumed to have a sensitivity and specificity of 100%). Patients correctly identified as having functionally significant stenosis (“true positive” result) will progress to revascularisation, while patients correctly identified as having non-significant coronary stenosis (“true negative” result) will receive optimal medical therapy without the need for revascularisation. However, patients incorrectly identified as having functionally significant stenosis (“false positive” result) will lead to unnecessary revascularisations, while patients incorrectly identified as not having functionally significant stenosis (“false negative” result) will not receive an appropriate revascularisation procedure and, as a result, may experience reduced quality of life and increased risk of major cardiovascular event or death until their disease is correctly managed. The tests may also lead to inconclusive results about the functional significance of stenosis, which can lead to further invasive testing with pressure-wire FFR/iFR in order to confirm whether or not there is a need for revascularisation.

Establishing a direct link between diagnostic test accuracy and clinical outcomes is unlikely to be feasible due to limited or no formal evidence. The longer-term impact and subsequent prognosis associated with the diagnostic outcomes will be modelled using the best available evidence on the risk of major cardiovascular events such as myocardial infarction and sudden cardiac death, as well as adverse events related to revascularisation, surgery and diagnosis. The model will also consider

how specific patient baseline characteristics and risk affect the likelihood of experiencing further cardiovascular events and need for revascularisation.

Consideration will be given to modelling the harmful effects associated with radiation exposure from invasive FFR measurement. The robustness of the analysis will depend on the availability of evidence linking radiation exposure to cancer risk, as well as the effect of cancer on quality-adjusted life expectancy. This will be informed using targeted literature searches to identify the increased risk of cancer as a result of ionising radiation from ICA with pressure-wire FFR/iFR and revascularisation procedures.

It will also be important to consider patient throughput and its impact on the cost per patient for the use of the QAngio XA 3D/ QFR and CAAS vFFR imaging software. The implication of variation in patient throughput is likely to be explored using sensitivity and threshold analysis. It will also be important to consider whether the provision of the non-invasive FFR/iFR measurement might influence physician practice and referral behaviour in the management of stable angina and any possible implications for throughput.

Model parameters

Further details of the model structure and data to be used to populate the model will be dependent on the findings from the systematic searches of the literature. However, it is expected that particular consideration will be given to the following key variables:

- Diagnostic accuracy of the different technologies;
- Time to QFR, vFFR and FFR/iFR measurement;
- Resource utilisation and costs for the different technologies (including acquisition costs, consumables, maintenance, staff and training costs);
- Size of the relevant population and anticipated throughput for each technology;
- The number of revascularisations;
- The risks of major cardiovascular events (including myocardial infarction and sudden cardiac death);
- The short- and long-term costs and consequences of stable angina (including related cardiovascular events);
- Adverse events related to both diagnostic and treatment interventions;
- The link between radiation exposure and cancer risk and mortality;
- Health related quality of life impact resulting from the different technologies.

Costs and resource utilisation

Resource utilisation and costs will be estimated for the QAngio XA 3D/ QFR and CAAS vFFR imaging software and pressure-wire guided FFR measurement, including hyperemia inducing agents, as well as costs of treatment intervention, managing major adverse cardiac events and other adverse events. The costs are expected to include:

- Costs of QAngio XA 3D/ QFR and CAAS vFFR imaging software (including purchase price of software, software installation, support, maintenance and training costs, and potential need for a new workstation, time to process results)

- Costs of invasive functional assessment of stenosis (including pressure wires and hyperemia inducing agents)
- Costs of revascularisation (including PCI and CABG)
- Costs of drug treatment for optimal medical therapy
- Costs of managing major adverse cardiac events (including MI and sudden cardiac death)
- Costs of managing adverse side effects related to invasive functional assessment, medical therapy, revascularisation (PCI or CABG) and radiation exposure.

Data for the cost analysis will be obtained from routine NHS sources, published studies and information provided by the manufacturers of the devices.

Economic analysis objectives

The specific objectives of the cost-effectiveness analysis are:

- To structure an appropriate decision model to characterise existing care pathways and the subsequent impact of QAngio XA 3D/ QFR and CAAS vFFR imaging software during ICA for the functional assessment of coronary obstructions for people with stable angina, whose angiograms show intermediate coronary stenosis.
- To populate the model using the most appropriate data, identified systematically from published literature, routine data sources and potentially using data elicited from relevant clinical experts and manufacturers.
- To relate intermediate outcome measures of diagnostic accuracy to subsequent revascularisation decisions and to final health outcomes, including morbidity and mortality associated with revascularisation and major cardiovascular events. Final health outcomes will be evaluated in terms of QALYs. This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to their additional cost, in units which permit comparison with other uses of health service resources.
- To estimate the incremental cost-effectiveness of the QAngio XA 3D/ QFR and CAAS vFFR imaging software during ICA compared with visual assessment of ICA alone, or ICA followed by FFR/iFR if ICA is inconclusive, based on an assessment of the long-term NHS and Personal Social Service costs and quality-adjusted survival. The time horizon of the model will be sufficient to capture both the short-term and longer-term outcomes. The final specification of the model will be determined during the review and model conceptualisation stage.
- To characterise the uncertainty in the data used to populate the model and to present the resulting uncertainty in the results to decision makers. A probabilistic model will be developed which requires that, where possible, uncertainty in inputs are reflected through the use of appropriate probability distributions, rather than as a fixed parameter input. Using Monte Carlo simulation, this parameter uncertainty will be translated into uncertainty in the overall results. This will be presented graphically using cost-effectiveness acceptability curves, which show the probability that an intervention is expected to be cost-effective for a given estimate of health opportunity costs (cost-effectiveness threshold).
- To undertake sensitivity, scenario and/ or threshold analysis to explore the robustness of the cost-effectiveness results to changes in the parameter inputs (e.g., impact of increasing/

decreasing sensitivity and specificity of the diagnostic images), structural assumptions of the model and the time horizon.

It is anticipated that the model will be developed in either Microsoft Excel or the statistical programming language of R (or a combination of both e.g., separate software may be used for the diagnostic and treatment elements of the model); the choice of software will depend on the final conceptualisation of the model.

Handling information from the companies

Any 'commercial in confidence' data provided by the manufacturers or study analysts and specified as such will be highlighted in blue and underlined in the assessment report. Any 'academic in confidence' data provided by the manufacturers or study analysts will be highlighted in yellow and underlined in the assessment report.

If confidential information is included in economic models then a version using dummy data or publically available data in place of confidential data will be provided.

Competing interests of authors

None of the authors have any conflicts of interest.

Timetable/milestones

Milestone	**Date to be completed**
Submission of final protocol	3 October 2019
Submission of progress report	3 January 2020
Submission of draft Diagnostic Assessment Report	28 February 2020
Submission of final Diagnostic Assessment Report	27 March 2020

References

1. Emori H, Kubo T, Kameyama T, Ino Y, Matsuo Y, Kitabata H*, et al.* Diagnostic Accuracy of Quantitative Flow Ratio for Assessing Myocardial Ischemia in Prior Myocardial Infarction. *Circ J* 2018;**82**:807-14. https://doi.org/10.1253/circj.CJ-17-0949
2. Mejia-Renteria H, Lee JM, Lauri F, van der Hoeven NW, de Waard GA, Macaya F*, et al.* Influence of Microcirculatory Dysfunction on Angiography-Based Functional Assessment of Coronary Stenoses. *JACC Cardiovasc Interv* 2018;**11**:741-53. https://doi.org/10.1016/j.jcin.2018.02.014
3. Xing Z, Pei J, Huang J, Hu X, Gao SJBjocs. Diagnostic Performance of QFR for the Evaluation of Intermediate Coronary Artery Stenosis Confirmed by Fractional Flow Reserve. 2019;**34**:165-72.

4. Westra J, Tu S, Campo G, Qiao S, Matsuo H, Qu X*, et al.* Diagnostic performance of quantitative flow ratio in prospectively enrolled patients: An individual patient-data meta-analysis. *Catheter Cardiovasc Interv* 2019; 10.1002/ccd.28283. https://doi.org/10.1002/ccd.28283
5. Götberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L*, et al.* Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. 2017;**376**:1813-23.

Appendix 1

Search strategy for MEDLINE

Database: Ovid MEDLINE(R) ALL <1946 to September 25, 2019>
Search Strategy:
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1 QANGIO$.ti,ab,kw. (8)
2 quantitative flow ratio$.ti,ab,kw. (36)
3 QFR.ti,ab,kw. (82)
4 "3D/QFR".ti,ab,kw. (1)
5 aQFR.ti,ab,kw. (2)
6 adenosine-flow QFR.ti,ab,kw. (2)
7 cQFR.ti,ab,kw. (6)
8 contrast-flow QFR.ti,ab,kw. (7)
9 fQFR.ti,ab,kw. (5)
10 fixed-flow QFR.ti,ab,kw. (5)
11 iQFR.ti,ab,kw. (1)
12 index QFR.ti,ab,kw. (1)
13 LQFR.ti,ab,kw. (4)
14 lesion QFR.ti,ab,kw. (1)
15 vQFR.ti,ab,kw. (1)
16 vessel QFR.ti,ab,kw. (1)
17 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (99)
18 vessel FFR.ti,ab,kw. (11)
19 vFFR.ti,ab,kw. (8)
20 CAAS vFFR.ti,ab,kw. (0)
21 18 or 19 or 20 (19)
22 17 or 21 (118)
23 animals/ not (humans/ and animals/) (4586208)
24 22 not 23 (107)
25 "quinol:fumarate reductase".ti,ab. (29)
26 24 not 25 (88)

Appendix 2

Draft data sharing agreement

(Supplied as a separate document)